Published in final edited form as:

Pediatr Infect Dis J. 2012 June ; 31(6): . doi:10.1097/INF.0b013e318253844b.

Impact of Human Immunodeficiency Virus Severity on Cognitive and Adaptive Functioning during Childhood and Adolescence

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Abstract

Background—The influence of disease severity on cognitive and adaptive functioning in perinatally infected youth with (PHIV+/C) and without (PHIV+/NoC) a previous AIDS-defining illness (CDC Class C event), compared to perinatally exposed but uninfected youth (PHEU) is not well understood.

Methods—This was a cross-sectional analysis of cognitive and adaptive functioning in PHIV+/C (n=88), PHIV+/NoC (n=270), and PHEU (n=200) youth aged 7 to 16 years, from a multi-site prospective cohort study. Youth and caregivers completed the Wechsler Intelligence Scale for Children (WISC-IV) and the Adaptive Behavior Assessment System (ABAS-II) respectively. We compared means and rates of impairment between groups, and examined associations with other psychosocial factors.

Results—Overall mean scores on measures of cognitive and adaptive functioning were in the low average range for all three groups. After adjustment for covariates, mean full scale IQ (FSIQ) scores were significantly lower for the PHIV+/C group than the PHIV+/NoC and PHEU groups (mean=77.8 vs 83.4 and 83.3, respectively), while no significant differences were observed between the PHEU and PHIV+/NoC groups in any domain. Lower cognitive performance for the PHIV+/C group was primarily attributable to a prior diagnosis of encephalopathy. No significant differences between groups were observed in adaptive functioning.

Conclusion—For long-term survivors, youth with HIV infection and a prior CDC class C event have higher risk for cognitive but not adaptive impairment regardless of current health status; this finding appears attributable to a previous diagnosis of encephalopathy. Early preventive therapy may be critical in reducing risk of later neurodevelopmental impairments.

Keywords

Cognitive functioning; adaptive functioning; pediatric HIV infection; perinatal HIV exposure

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Financial Disclosure: The authors have indicated that they have no financial relationships relevant to this article to disclose.

As the majority of youth with perinatally acquired HIV infection (PHIV+) are aging into adolescence and young adulthood, it is important to understand the long-term impact of HIV infection and concomitant risk factors on the cognitive abilities and adaptive functioning of these youth. Knowledge of individual strengths and vulnerabilities is critical for understanding quality of life and health issues, including current and future educational needs, appropriate career options, adherence, high-risk behaviors, and the likelihood of functional independence during adulthood.

Previous studies of PHIV+ children described global and specific effects of HIV on the central nervous system (CNS) and cognitive functioning, ranging in severity from pervasive to subtle, the most severe form being encephalopathy. With the advent of highly active antiretroviral therapy (HAART), the incidence of severe CNS impairment has decreased significantly,¹⁻³ yet only recently are neurocognitive profiles of HAART-experienced, older PHIV+ youth emerging. These studies suggest overall abilities in the low average to average range with specific deficits in areas such as working memory and executive functioning.³⁻⁸ Results from the few studies of adaptive functioning suggest decreased ability to function effectively within school and other social settings.⁹⁻¹²

Biomedical markers of virologic and immunologic status such as CD4+ T-lymphocyte count and percentage, CDC classification of HIV disease¹³, exposure to HAART, timing of HIV transmission, and HIV RNA viral load (VL) are key predictors in assessing risk for cognitive and adaptive impairment, even in older children^{5,8,11,12,14-18}. In particular, studies suggest that an early AIDS-defining illness and current or nadir CD4 count are associated with cognitive or adaptive impairment in older HIV+ youth.^{6,8,11,18}

However, earlier studies linking HIV disease severity and neurobehavioral abilities in school-aged children were limited by small sample sizes, absent or inadequate comparison groups, and thus inability to evaluate the potential confounding effects of demographic and psychosocial factors that may negatively affect the long-term outcome of these youth. The aim of this study was to examine the cognitive and adaptive functioning of a large group of PHIV+ youth and a cohort of youth who were perinatally HIV-exposed but uninfected (PHEU) who share similar demographic and psychosocial characteristics. We hypothesized that PHIV+ school-aged youth with a prior AIDS diagnosis (i.e. CDC Class C) would have the greatest deficits in cognitive and adaptive functioning, while PHIV+ youth without CDC Class C diagnoses would have similar functioning to PHEU youth of similar backgrounds. We also aimed to identify biological, demographic, and psychosocial factors associated with poor cognitive and adaptive functioning.

Methods

Study Population

Data for these analyses come from the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS), a prospective study evaluating the impact of HIV infection and antiretroviral therapy (ART) on perinatally HIV-infected and HIV-exposed youth. PHIV+ and PHEU youth were enrolled at 15 AMP sites in urban areas of the U.S., including Puerto Rico. AMP eligibility criteria included: 1) perinatal HIV exposure; 2) ages 7-16 years; 3) English or Spanish speaking; and 4) among PHIV+ participants, engaged in medical care with available ART history.

Procedures

Institutional Review Boards (IRBs) at all participating sites and the Harvard School of Public Health approved the study. Parent(s) or legal guardians provided written informed

consent for child and caregiver participation. Caregivers were not required to enroll in the study. Youth provided assent based on age and local IRB guidelines. Consented youth and caregivers were seen every six months for medical, clinical, and neuropsychological evaluations. Evaluations were administered in English or Spanish (when a psychologist fluent in Spanish and Spanish versions of measures were available). All child data and household demographics for this analysis were collected at the entry visit. Caregiver measures were collected six-months post-study entry.

Outcome Measures

Cognitive Functioning—The Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) ¹⁹ is a measure of intelligence for individuals aged 6 to 17 years, with 10 core subtests yielding scores reflecting ability in four domains of cognitive functioning: Verbal Comprehension (VC), Perceptual Reasoning (PR), Working Memory (WM), and Processing Speed (PS). Raw scores are converted into age-related subtest standard scores for each domain, then combined to yield a Full Scale Intelligence Quotient (FSIQ). The reference mean for the FSIQ and each domain composite score is 100, with a standard deviation (SD) of 15.

Adaptive Functioning—The Adaptive Behavior Assessment System- Second Edition (ABAS-II) ²⁰ is a measure of adaptive abilities for individuals between the ages of 5 and 21 years. The 240 items were administered via face-to-face interview with the parent/caregiver to obtain responses regarding youth performance of a particular skill. Scaled scores are computed in nine skill areas and combined into composite scores for Conceptual (CON), Social (SO), and Practical (PR) domains and a General Adaptive Composite (GAC). The reference mean for the CON, SO, PR and GAC is 100, with a SD of 15.

Measurement of Covariates

Caregiver Functioning—Caregiver mental health and substance use were assessed with the Client Diagnostic Questionnaire (CDQ), a psychiatric screening tool designed and validated for populations affected by HIV. ²¹ The CDQ is a structured interview available in English or Spanish, and was used to identify current symptoms of psychiatric disorder(s), and alcoholic and non-alcoholic substance abuse. Caregiver cognitive status was evaluated with the Wechsler Abbreviated Scale of Intelligence (WASI), ²² a nationally standardized and reliable measure of intelligence for English speaking individuals, ages 6 - 89 years. The reference mean for FSIQ, Verbal IQ (VIQ) and Performance IQ (PIQ) is 100, with a SD of 15.

Demographic and Health Information—Child and caregiver demographic and health information were obtained via examination, interview, and chart abstraction, and included: child age, sex, race/ethnicity, primary language, and for youth with HIV infection, study-entry and peak HIV-1 RNA viral load, nadir and current CD4+ T lymphocyte count and percent, CDC Classification of HIV disease, and previous diagnosis of encephalopathy. Diagnoses of encephalopathy were previously reviewed and confirmed by a pediatric neurologist. For purposes of this analysis, no differentiation was made between static and progressive encephalopathy. Caregiver demographics included relationship to child, education, and income.

Statistical Methods

Based on our a priori statistical analysis plan, we classified the study cohort into three groups: PHIV+ youth with a previous Class C diagnosis (AIDS-defining illness) (PHIV+/C), PHIV+ youth with no prior CDC Class C diagnosis (PHIV+/NoC), and PHEU. Comparisons

of demographic variables between the three groups at study entry were performed using Kruskal-Wallis and Chi-square tests.

Group differences in cognitive and adaptive functioning were explored by comparing overall and subtest mean scores and by comparing rates of impairment, defined as a standard score <70 (two standard deviations below the reference mean). We used generalized estimating equation (GEE) methods to model mean scores in unadjusted linear regression models and then adjusting for potential covariates including: age group (<12y vs. ≥12y), non-white race, Hispanic ethnicity, primary language (Not English vs. English), caregiver relationship (biological parent vs. not), household income (<\$20,000 vs. ≥\$20,000), caregiver education (high school graduate vs. not), caregiver psychiatric or substance use problem vs. not, and caregiver cognitive function (not impaired vs. impaired). Reduced models for FSIQ and GAC were built using a group stepwise algorithm with $p < 0.20$ to enter the model and $p < 0.15$ to remain in the model at subsequent steps. The reduced models for FSIQ and GAC were then applied to all WISC-IV and ABAS-II scales, respectively. For the impairment outcomes, unadjusted and adjusted logistic regression methods were used to assess differences among study groups, building full and reduced models similarly to the linear regression models.

Concordance between cognitive and adaptive functioning within the three groups was assessed with the Pearson correlation coefficient for mean scores. The proportion with agreement (either both FSIQ and GAC <70 or both ≥70) was estimated within the three study groups and overall. McNemar's test was used to assess asymmetry of outcomes (<70, ≥70).

Sensitivity analyses were performed by repeating prior models after excluding youth with a previous diagnosis of encephalopathy to examine the contribution of having a diagnosis of encephalopathy on the overall Class C effect. For participants with HIV, we also explored the association between mean scores and impairment outcomes and other markers of disease severity: age at which most severe CDC classification was reached, nadir and entry CD4%, and peak and entry VL (copies/ml).

A two-sided p-value of 0.05 was considered statistically significant. SAS v9.1 (SAS Institute Inc, Cary, NC) was used for all analyses.

Results

As of April 1, 2010, 678 children were enrolled in AMP. Among those, 558 (82%) had a valid WISC-IV and ABAS-II evaluation, including 88 in the PHIV+/C group, 270 in the PHIV+/NoC group, and 200 in the PHEU group. Tables 1 and 2 summarize the child, family, and health characteristics of the study cohort, stratified by infection status. Antiretroviral (ARV) regimens at study entry, including drug class and number of ARVs were compared; no differences existed between the PHIV+/C and PHIV+/NoC groups.

Hispanic ethnicity was the only variable significantly different between those with missing outcome data (120/678, 18%) versus those with valid measures, likely due to restrictions in test administration for non-English speaking participants in PHACS. IQ and psychiatric/substance use data were missing for 41% and 28% of caregivers, respectively. Reasons included: caregiver not enrolled, refusal, insufficient time, and non-English primary language.

Cognitive Functioning

On average, cognitive functioning of PHIV+/C, PHIV+/NoC, and PHEU youth was in the low average range compared to the WISC-IV normative sample, with an overall mean of 86.2 (SD=15.6). Significantly lower mean scores were observed for the HIV+/C group than the other two groups in both unadjusted and adjusted analyses (Table 3). After adjustment for covariates, the FSIQ, PR, and PS mean scores for the PHIV+/C group were approximately 6 points lower than the PHIV+/NoC and PHEU groups, while no significant difference was observed between the PHIV+/NoC and PHEU groups in any domain.

A significantly greater percentage of children in the PHIV+/C group demonstrated impaired cognitive functioning (FSIQ<70) (24.4%) compared to the PHIV+/NoC (8.6%) and PHEU (12.1%) groups (Figure 1). There was a two- to five-fold increase in the risk of impairment for the HIV+/C group compared to the PHEU group in FSIQ, PS, PR, and WM. These group differences remained after adjusting for covariates. In addition, a significantly increased odds of VC impairment was observed after adjustment (See Table, Supplemental Digital Content 1).

Adaptive Functioning

Adaptive functioning of PHIV+/C, PHIV+/NoC, and PHEU youth was in the average range (GAC mean of all groups: 91.8; Table 3). Subdomain mean scores were also not significantly different between groups in the adjusted or unadjusted GEE models and were approximately seven points below the reference mean (See Figure, Supplemental Digital Content 1). Rates of impairment for GAC were 12.5%, 8.2%, and 12%, respectively. There was a three-fold increased odds of impairment in Practical skills for the HIV+/C group in both unadjusted and adjusted models (See Table, Supplemental Digital Content 1).

Discordance in Cognitive and Adaptive Functioning

Relatively high rates of agreement between cognitive (FSIQ) and adaptive (GAC) functioning were observed in the PHIV+/C (78%), PHIV+/NoC (89%), PHEU (82%) groups. Concomitant impairment (<70) in both cognitive and adaptive functioning was observed among 7% of PHIV+/C youth and 3% of PHIV+/NoC and PHEU youth. The rate of discordance between cognitive and adaptive functioning was higher for the PHIV+/C group, who were more likely to demonstrate impairment in cognition but not adaptive functioning, relative to other groups (McNemar Test p-value=0.01).

Factors Associated with Cognitive and Adaptive Functioning

Factors associated with lower FSIQ in the adjusted linear and logistic regression models included Class C diagnosis, non-white race, primary language (non-English), and caregiver with a significant cognitive impairment or missing cognitive data. In the adjusted linear model, higher cognitive scores were associated with having a biologic parent as caregiver and having higher household income. Older age and Hispanic ethnicity were associated with lower cognitive scores, but these associations did not persist after adjustment for other factors.

After adjustment, lower adaptive functioning (GAC) was associated with male sex and missing caregiver CDQ data, while older age at entry was associated with better functioning. The adjusted logistic regression model supported this; older age at study entry was associated with decreased risk of poor adaptive functioning.

HIV Disease Markers

In adjusted models, measures of HIV disease severity were consistently associated with cognitive and/or adaptive outcomes. Peak VL >100,000 copies per million (cpm) was associated with decreased mean scores in all domains of cognitive functioning. Nadir CD4% <15% was consistently associated with lower scores in all domains of adaptive functioning. CD4% <15% at study entry was associated with significantly lower scores on FSIQ, VC, and PR.

Encephalopathy

Encephalopathy was diagnosed in 42 participants; 70% prior to age 3 years. After excluding participants with encephalopathy of any etiology (6 non-HIV related) in a post-hoc analysis, we observed no significant differences in unadjusted or adjusted WISC-IV or ABAS-II global or domain mean scores between the PHIV+/C (no encephalopathy), PHIV+/NoC, and PHEU groups. Mean scores (unadjusted) were significantly lower for all cognitive domains for the encephalopathic group (See Figure, Supplemental Digital Content 2). However, youth in the HIV+/C group (but no encephalopathy) had a three-fold higher odds for impairment in Processing Speed ($p=0.04$).

Discussion

This is the first study to assess the association of HIV disease severity with both cognitive and adaptive functioning among a large cohort of older youth with perinatal HIV infection, and a well characterized comparison group of perinatally HIV exposed youth with a rich historical database. Our findings concur with previous studies indicating that early severe HIV disease significantly increases the risk for neurocognitive impairment.^{6,8,18} However, our results expand existing knowledge by specifically implicating a previous diagnosis of encephalopathy in the observed effects. We found that youth with perinatal HIV infection and a previous AIDS-defining illness demonstrated significantly greater delays in cognitive functioning than those without a prior AIDS-defining illness as well as their HIV-exposed but uninfected peers. This finding remained after controlling for a number of potentially influential environmental variables.

A diagnosis of encephalopathy during development greatly increased the risk for significant impairment in general cognitive functioning as well as in Processing Speed, Perceptual Reasoning, and specific adaptive domains, observed years after the neurologic diagnosis. Despite these cognitive deficits, no group differences in immunologic or virologic markers existed at study entry, suggesting long-term viral suppression and immune reconstitution, and recovery from early and severe HIV-related biologic events via ART. Thus, the CNS may have less resilience or recovery potential, even after a protracted period, particularly when encephalopathy occurs before age 3 as was the case for the majority of PHIV+/C participants with that diagnosis. Youth with early, severe CNS events may be those infected *in utero*, and/or with exposure to higher viral loads earlier in the perinatal process, with resulting aberrations to brain development, even before the Class C event²³. This concurs with previous findings that those infected earlier in the perinatal process were likelier to demonstrate early symptoms of AIDS,²³ and higher risk for later neurocognitive impairment.²⁵

Youth with a Class C event but no encephalopathy were at an increased risk for impairment in Processing Speed relative to their healthier or uninfected peers, despite comparability in all cognitive and adaptive mean scores. This supports the findings of other studies of adults with HIV infection regarding the vulnerability of processing speed in HIV-infected individuals.²⁶⁻²⁷

Youth in this cohort, including PHEU youth, obtained mean scores in the low average range, particularly in the cognitive domains. This analysis controlled for many biologic and environmental factors that may have a moderating effect on these outcomes. Prior investigations have detailed the importance of caregiver/family characteristics in a youth's development. In this study as well, better cognitive outcome was associated with having a biologic parent as caregiver, higher family income level, and higher caregiver cognitive functioning. Factors associated with poorer cognitive outcome included being non-white, having a primary language other than English, and older age at study entry. Associations with poorer adaptive functioning included male sex, and having a caregiver who did not complete the psychiatric interview, while older age was associated with better adaptive functioning. The possible contributions of *in utero* HIV and/or ARV exposure on the neurodevelopment of the PHEU youth can also not be ruled out as moderating factors. Although a non-HIV and non-ARV exposed cohort may more fully elucidate exposure effects, this investigation's group of PHEU youth provides a socio-demographically comparable cohort to answer the question regarding effects of HIV infection.

Unique contributions of this study include the investigations of adaptive functioning and the relationship between adaptive and cognitive functioning in PHIV+ youth. Knowledge of youth adaptive functioning broadens our appreciation of the impact of HIV disease on their ability to function effectively in multiple milieus, including social, home, school and community. Our results suggest that the majority of youth have adequate skills to manage the demands of everyday life, regardless of past severe illness or cognitive functioning. We interpret these findings with some caution, however, given their reliance on caregiver report. In addition, caregivers of youth who experienced early symptoms of severe disease may have different expectations for their child's behavior and abilities than those who were relatively symptom free throughout their lives. Methodological differences (e.g. route of infection, lack of control group, small sample sizes, age of cohort) make findings from earlier studies, which identified associations between HIV infection and lower adaptive functioning, difficult to interpret in relation to our results.

Limitations of this analysis include the cross-sectional design, limiting our ability to examine causal relationships and trends in functioning over time. Second, the adaptive functioning outcome was based on caregiver report, rather than by direct assessment or multiple data sources. Next, this cohort may not fully represent the population of HIV-affected youth in the U.S. Eligibility for this study included previous enrollment in an HIV-related research study, implying a level of follow-up, including multiple exposures to neuropsychological assessment that may be uncommon for most youth exposed to HIV. Finally, the diagnosis of encephalopathy was based on retrospective chart review and may be an underestimate due to variation in clinician diagnostic practices.

Conclusions

We conclude that large longitudinal studies examining trends in specific domains of cognitive and adaptive functioning of HIV-exposed and HIV-infected youth are needed to further define causal pathways of impairment, as well as factors that mediate the relationship between disease markers and neurocognitive and functional outcomes during adolescence and adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The study was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development with co-funding from the National Institute of Allergy and Infectious Diseases, the National Institute on Drug Abuse, the National Institute of Mental Health, the National Institute of Deafness and other Communication Disorders, the National Heart Lung and Blood Institute, National Institute of Neurological Disorders and Stroke, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard University School of Public Health (U01 HD0522102-04) and the Tulane University School of Medicine (U01 HD 052104-01).

We thank the children and families for their participation in PHACS, and the individuals and institutions involved in the conduct of PHACS. The study was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with co-funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute of Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, and the National Institute on Alcohol Abuse and Alcoholism through cooperative agreements with the Harvard University School of Public Health (HD052102) (Principal Investigator: George Seage; Project Director: Julie Alperen) and the Tulane University School of Medicine (HD052104) (Principal Investigator: Russell Van Dyke; Co-Principal Investigator: Kenneth Rich; Project Director: Patrick Davis). Data management services were provided by Frontier Science and Technology Research Foundation (PI: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (PI: Julie Davidson). The following institutions, clinical site investigators and staff participated in conducting PHACS AMP in 2010, in alphabetical order: **Baylor College of Medicine:** William Shearer, Norma Cooper, Lynette Harris; **Bronx Lebanon Hospital Center:** Murlu Purswani, Mahboobullah Baig, Anna Cintron; **Children's Diagnostic & Treatment Center:** Ana Puga, Sandra Navarro, Doyle Patton; **Children's Hospital, Boston:** Sandra Burchett, Nancy Karthas, Betsy Kammerer; **Children's Memorial Hospital:** Ram Yogev, Kathleen Malee, Scott Hunter, Eric Cagwin; **Jacobi Medical Center:** Andrew Wiznia, Marlene Burey, Molly Nozyce; **St. Christopher's Hospital for Children:** Janet Chen, Elizabeth Gobs, Mitzie Grant; **St. Jude Children's Research Hospital:** Katherine Knapp, Kim Allison, Patricia Garvie; **San Juan Hospital/Department of Pediatrics:** Midnela Acevedo-Flores, Heida Rios, Vivian Olivera; **Tulane University Health Sciences Center:** Margarita Silio, Cheryl Borne, Patricia Sirois; **University of California, San Diego:** Stephen Spector, Kim Norris, Sharon Nichols; **University of Colorado Denver Health Sciences Center:** Elizabeth McFarland, Emily Barr, Robin McEvoy; **University of Maryland, Baltimore:** Douglas Watson, Nicole Messenger, Rose Belanger; **University of Medicine and Dentistry of New Jersey:** Arry Dieudonne, Linda Bettica, Susan Aduabato; **University of Miami:** Gwendolyn Scott, Lisa Himic, Elizabeth Willen Note: The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health or U.S. Department of Health and Human Services.

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Figure 1. Unadjusted Rates of Cognitive Impairment: % Scoring 2 SD Below the Mean
 PHIV+/NoC=Perinatal HIV infection with no CDC Class C event; PHIV+/C=Perinatal HIV infection with a prior CDC Class C event; PHEU=Perinatally HIV Exposed but uninfected; FSIQ=Full Scale Intelligence Quotient